REMARKS

Applicants are filing the instant Amendment in order to place the claims in condition for allowance. Applicants therefore request entry of the Amendment.

Remarks to the Title

Amendments to the Title correct a typographical error. Applicants assert that no new matter has been introduced.

Status of Claims

Claims 21-37 are pending in the application. Claims 21-29 have been rejected, and claims 30-37, submitted in the Response dated February 4, 2008, were not entered by the Examiner in the Advisory Action dated May 14, 2008. Amendments to claims 23-26 are clerical in nature and introduce no new matter. Support for amended claim 21 can be found throughout the application as originally filed and specifically in claim 22 in the preliminary amendment that was filed with the original application. Applicants assert that no new matter has been introduced.

New claims 38-44 have been added. Support for claim 38 can be found throughout the application as originally filed and specifically in claim 26 as originally filed. Support for claims 39-42 can be found throughout the application as originally filed and specifically in paragraph 48. Support for claim 43 can be found throughout the application as originally filed and specifically in paragraph 51. Support for claim 44 can be found throughout the application as originally filed and specifically in paragraph 53. Applicants assert that no new matter has been introduced.

Claims 22, 27, and 28 have been canceled without prejudice or disclaimer. In making this cancellation without prejudice, Applicants reserve all rights in these claims to file divisional and/or continuation patent applications.

The Telephone Interview

Applicants thank the Examiner, Dr. Jeffrey Parkin, for granting and attending the telephone interview, with Applicants' Representative, Dr. Cheryl Schindler, Reg. No. 59,848 on July 9, 2008 in view of significant scheduling difficulties and minor technical problems and for considering the proposed claim amendments and new claims. In the interview, the Examiner indicated that claims 21, 23-26, and 29-36 as submitted in the response dated February 4, 2008 would be allowable if a terminal disclaimer was filed to the priority application, United States Patent Number 6,099,848.

Double Patenting Rejections

Applicants attach hereto a terminal disclaimer to priority application United States Patent Application Serial Number 08/972,902, now United States Patent 6,099,848.

35 U.S.C. § 112 Rejections

In the Advisory Action dated December 27, 2007, the Examiner maintained his rejection of claims 21-29 under 35 U.S.C. § 112, first paragraph, as allegedly lacking support for auxotrophic attenuated Listeria strains. Applicants disagree. Claims 21, 23-26, 29, and 38-44 describe the use of the dal/dat auxotrophic attenuated Listeria strain, for which there is description regarding its preparation and use in the examples described in paragraphs [0080]-[0110]. A skilled artisan would have no difficulty understanding based on the description provided in the instant specification that Applicants had possession of the dal/dat auxotrophic

attenuated Listeria strain and would be able to make and/or use a dal/dat Listeria auxotroph for inducing an immune response against a cancer cell without undue experimentation. The Examiner stated in the Office Action dated June 14, 2007 that appropriately drafted claim language directed toward this embodiment [dal-/dat- double-mutant] would be acceptable (page 5), and reiterated this as well in the Inteviews of December 19, 2007 and July 9, 2008. Applicants therefore request withdrawal of the rejections.

Applicants assert that they have also demonstrated possession and enablement for claims directed to a method of inducing an immune response against a cancer cell in a mammal via administration of an auxotrophic attenuated strain of *Listeria* comprising a heterologous cancer cell antigen. Applicants demonstrated possession by exemplifying a method of inducing an immune response in a mammal using a particular auxotrophic *Listeria* as an example (see paragraphs 0106-0110). Applicants have also provided written description of other auxotrophic mutations (see paragraph 0040), a description of how to generate auxotrophic mutants and methods to test for their auxotrophic phenotype (see paragraphs 0037-0039, 0049-0057, 0079-0088, and 0092-0097), and methods to test for the immunogenicity of auxotrophic *Listeria* strains (see paragraphs 0057-0058 and 0090-0091). In addition, auxotrophic mutants were known in the art, and the level of skill in the art of microbiology and specifically *Listeria* microbiology is very high, such that the generation of mutants is considered routine in the art (Marquis et al, Infect Immun. 1993 Sep;61(9):3756-60; Camilli et al, J. Bacteriol. 1990 Jul;172(7):3738-44 attached in the response dated October 31, 2007; Alexander et al. Infect Immun 61.5 (1993): 2245-8, attached in the

response dated October 31, 2007). Therefore, it would be clear to a person skilled in the art that the inventors had possession of the claimed invention.

The Examiner alleged that "the disclosure fails to describe the generation of other suitable strains and fails to provide a reproducible means for obtaining said strains." As described above, Applicants provide numerous methods in the specification that would allow a person with ordinary skill in the art to generate auxotrophic *Listeria* strains.

The Examiner further alleged that the subject specification does not provide support for other strains that are attenuated and highly immunogenic. However, examples of such strains were known in the art at the time of filing (for e.g., Alexander et al., 1993). In addition, the level of skill and knowledge in the art at the time of filing would have allowed a person skilled in the art to generate auxotrophic attenuated strains that are highly immunogenic for use as live vaccine vehicles, as was demonstrated by Alexander et al. 1993. Examples of methods that a person of ordinary skill in the art may use to render the auxotrophic strains more immunogenic are disclosed in the subject specification (paragraphs 0061-0063) and were known in the art.

The Examiner also alleged that the disclosure appears to suggest that double mutants are required to practice the invention. Applicants disagree. *Listeria* strains comprising a mutation in at least one gene whose protein product is essential for growth of attenuated *L. monocytogenes* strains that can be used as vaccine vehicles are disclosed in the subject specification (see paragraphs 0038 and 0040), in the references described *supra*, and in other references (for example, Rouquette et al. FEMS Microbiol Lett 133.1-2 (1995): 77-83 attached in the response dated October 31, 2007). Thus, it is clear that a double mutant is not necessary in all cases to obtain an auxotrophic mutant and/or to practice the invention.

Applicants thank the Examiner who appears to have accepted Applicants' arguments from the response to office action dated March 22, 2007 that a person skilled in the art would be able to substitute the attenuated auxotrophic strains known in the art, such as those described by Camilli et al. and Marquis et al. for the auxotrophic strains described in the subject specification, as the Examiner has not provided a rebuttal.

Applicants further assert that the specification is fully enabling for claims directed to a method of inducing an immune response against a cancer cell in a mammal via administration of an auxotrophic attenuated strain of *Listeria* comprising a heterologous cancer cell antigen. Working examples for making and using attenuated auxotrophic mutant strains (see paragraphs 0107-0111) are provided, including detailed methodology to curtail the time required to carry out the generation of attenuated auxotrophic *L. monocytogenes* mutants (see paragraphs 0037-0039 and 0049-0057 and 0061-0063), providing the necessary amount of direction or guidance for a skilled artisan to generate auxotrophic mutants. Further, the state of the art at the time of filing would have enabled a person skilled in the art to generate other attenuated auxotrophic mutants (see, for example, Alexander et al. Infect Immun 61.5 (1993): 2245-8). Thus, based on the Wand's factors, the breadth of the claims is fully supported by the specification as filed based on the knowledge in the art at the time of filing.

The Examiner conceded that while it is possible to generate additional auxotrophic mutants, it is allegedly unclear which of these mutants will remain sufficiently attenuated to not cause disease, but still allow expression and presentation of the immunogen of interest. Again, the specification describes methods of evaluating attenuated *Listeria* (see paragraphs

0037-0039, 0049-0057, 0079-0088, and 0092-0097), of evaluating immunogenicity of *Listeria* (paragraphs 0057-0058 and 0090-0091), and examples of such attenuated, immunogenic strains were presented in the specification (paragraphs 0106-0110) and were known in the art (Alexander et al. 1993). Thus, it would not entail undue experimentation to generate, identify, and use appropriate auxotrophic mutants.

The Examiner alleged that the disclosure fails to describe the generation of other suitable strains or to provide a single working embodiment other than the dal⁻/dat⁻ double mutant. Applicants respectfully disagree and assert that the specification provides an enabling description of auxotrophic attenuated strains of *Listeria* other than dal and dat strains and their generation (paragraphs, 009, 0037, and 0040), thus describing the generation of other suitable strains.

The Examiner alleged that Marquis et al. (Infect Immun 61.9 (1993): 3756-60) and Portnoy et al. (US-Patent No. 5830702. November, 3, 1998) allegedly describe challenges involved in generating attenuated, auxotrophic *Listeria* mutants with the desired biological properties. More specifically, the Examiner indicated that Portnoy et al. allegedly states that certain nutritional auxotrophs may not be easily attenuated, and that Marquis et al. notes that transposon insertion auxotroph mutants were virulent and grew similarly to the parental strain and that the intracellular milieu of eukaryotic cells is a nutritious niche that allows the propagation of *Listeria* mutants. However, the specification (see paragraphs 0102 and 0103 and 0037) and the prior knowledge in the art (Alexander et al. 1993) clearly report success in generating auxotrophic attenuated mutants that are avirulent and are used to protect the host from *L. monocytogenes*-related disease. Applicants note that it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to

obtain a generic claim, provided that the effect was sufficiently demonstrated to characterize a generic invention. See Capon v. Eshar (418 F 3d 1349 (Fed Cir 2005)). In this case, the method exemplified in dal/dat mutants would certainly lead a skilled artisan to use the method in other auxotrophic mutants. In view of the foregoing arguments, Applicants respectfully assert that claims directed to a method of inducing an immune response against a cancer cell in a mammal via administration of an auxotrophic attenuated strain of *Listeria* comprising a heterologous cancer cell antigenare proper under 35 U.S.C. 112.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

APPLICANT(S): FRANKEL, Fred R et al.
SERIAL NO.: 10/660,194
FILED: September 11, 2003
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Dated: July 10, 2008

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